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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,259	07/24/2007	Karl Erik Hellstrom	440075.401USPC	1849

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,259	HELLSTROM ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *17-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/24/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-16) in the reply filed on October 12, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-26 are pending.

Claims 17-26, drawn to non-elected inventions and are not examined on the merits.

Claims 1-16 are examined on the merits.

Claim Objections

3. Claims 1, 2, 5, 7 and 12 are objected to because of the following informality: they reference accession numbers, which are subject to change at any time. Applicants have corresponding SEQ ID numbers, which are appropriate. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

The specification, however, does not disclose distinguishing and identifying features of a representative number of a genus comprising a portion of SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 10 expressed on a tumor cell and within a pharmaceutical composition to which the claims are drawn. The claims

and the specification seem to be remiss of a correlation between the structure of the said truncated and its recited function, inducing anti-tumor immunity with a cell surface form of an antibody, or antigen-bind fragment thereof, that binds specifically to CD137 so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus. Moreover, the specification fails to disclose which chemical structures are essential to the function of the epitopes found in the claimed truncated peptides can be ascertained/maintained. Thus, the specification fails to adequately describe at least a substantial number of members of the genus of fragments and antigens. As evidenced by Greenspan et al. (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope", see page 937, column 2. According to Greenspan, an epitope will include residues that make contact with a ligand but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes (of an antigen) that can elicit an antibody response to a given pathogen can only be identified empirically.

Furthermore, these methods also do not identify those microbial that have cross-reactivity with an apoptotic cell epitope. The art recognizes that

defining epitopes is not easy and there is a confusing divergence between the textbook definition of epitope and the definition that is in use in published descriptions of experimental investigations (Greenspan et al, Nature Biotechnology 17:936-937, 1999). Even as late as 2005 the art recognized that single-scale amino acid propensity profiles could not be used to predict epitope location reliably (Blythe et al. Protein Science 14:246-248, 2005). Therefore, even with art tools, it would be unpredictable to use those tools to attempt to identify conserved regions that were important for eliciting anti-tumor immunity as claimed.

All of the current claims encompass a genus of peptides, which are different from those disclosed in the specification, see page 79, lines 9-12. In the instant case, the claims comprise amino acid molecules other than SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 10. These genus of peptides comprising the said sequences and fragments and portions, thereof are not adequately described in the specification. The genus includes variants for which no written description is provided in the specification. Applicants' claims read on epitope fragments and antigens, which comprises hundreds of different possibilities. Here, no common element or attributes of the sequences are required. And furthermore the claims that relate to the fragments do not set forth a function. There are an unlimited number of sequences that meet the broad scope of the claims. The only limitations are the ability of these claimed peptides to induce anti-tumor immunity, however the claims does not establish which residues of

SEQ ID NO: 2, 6 or 10 and fragments thereof retain this activity. The specification has not identified or clearly set forth the function or structure of these plethora of peptides, which are continually being discovered. No structural limitations, functional limitation or requirements, which provide guidance on the identification of the sequences, which contain parts of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10 and their fragments, is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, Applicants intend to implement the defined sequences, as well as fragment molecules that can be administered to induce or enhance an immune response, see Examples 1-3 in the specification. However, these molecules and fragments thereof lack any specific structure and the function has not assured.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

The written description in this instant case only sets forth polypeptides, SEQ ID NO: 2, SEQ ID NO: 6 and SEQ ID NO: 10. The written description is not commensurate in scope with the claims drawn to portions of the said sequences that comprise arbitrary amino acid residues, undefined fragments and uncharacterized amino acid sequences is not commensurate scope with the established written description.

In the application at the time of filing, there is no record or description, which would demonstrate conception of any amino acid molecule other SEQ ID NO: 2, SEQ ID NO: 6 and SEQ ID NO: 10 which may or may not be capable of functioning in the manner suggested by the specification. Therefore, the claims fail to meet the written description requirement by encompassing

sequences, which are not described in the specification.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scholler et al. (Immunology 166: 3865-3872, 2001), and further in view of Hellstrom, K.E. et al. (J. Mol. Med. 81: 71-86, 2003)/ IDS Reference 1 on page 2 submitted July 24, 2007. Scholler teaches a composition comprising a portion of a cell surface CD83 polypeptide, as well as full-length CD83 expressed on human carcinoma cells, see abstract; CD83Ig fusion protein construction section on page 3865; and page 3866, Adhesion assays section. Absent evidence to the contrary the CD83 revealed in Scholler is the same as Applicants' amino acid sequences selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 10, which are CD83 polypeptides. Scholler teaches a first tumor cell expressing cell surface CD83 polypeptide on human carcinoma cells. Scholler does not teach a method of inducing anti-tumor immunity comprising the said carcinoma cells expressing an additional molecule that is a cell surface form of an antibody, or antigen-binding fragment

thereof that binds specifically to CD137. Scholler also does not teach a method of inducing anti-tumor immunity utilizing a composition comprising a first tumor cell that expresses a cell surface CD83 polypeptide and a second tumor cell that expresses a cell surface form of an antibody, antigen-binding fragment thereof, that binds specifically to CD137.

However, Hellstrom teaches a method for inducing anti-tumor immunity comprising transfecting "...tumor cells to express a cell-bound form of anti-CD137 single-chain Fv fragments (scFv)" in mouse models, see last ten lines of abstract on page 71; and page 79, Tumor...section. Furthermore, Hellstrom teaches transfecting K1735 melanoma cells with a cell-bound form of anti-CD137 scFv, reading on a second tumor cell. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce a composition comprising a tumor cell that expresses both a cell surface CD83 polypeptide and a cell surface form an antigen-binding fragment thereof that binds specifically to CD137 on tumor cells, as well as implementing two separate tumor cells expressing said molecules in an anti-tumor composition. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both documents, concomitant expression of stimulatory molecules induces immune responses, particularly CD8+ T cells, see Scholler's title and abstract; and Hellstrom, page 71 and 72. Hellstrom notes "...concomitant expression of tumor antigen and anti-CD137 scFv effectively engages NK cells, monocytes and dendritic cells, as

well as activated CD4+ and CD8+ T cells ...so as to induce and expand a tumor-destructive Th1 response", page 72, 1st two full sentences in column 1.

8. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scholler et al. (Immunology 166: 3865-3872, 2001), and further in view of Ye et al./ Nature Medicine 8(4): 343-348, April 2002/ IDS Reference 6 on page 2 submitted July 24, 2007. Scholler teaches a composition comprising a portion of a cell surface CD83 polypeptide, as well as full-length CD83 expressed on human carcinoma cells, see abstract; CD83Ig fusion protein construction section on page 3865; and page 3866, Adhesion assays section. Scholler discloses CD83 cloned into pLNCX vector, see page 3866. Absent evidence to the contrary the CD83 revealed in Scholler is the same as Applicants' amino acid sequences selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 10, which are CD83 polypeptides. Scholler teaches a first tumor cell expressing cell surface CD83 polypeptide on human carcinoma cells. Scholler does not teach a method of inducing anti-tumor immunity comprising the said carcinoma cells expressing an additional molecule that is a cell surface form of an antibody, or antigen-binding fragment thereof that binds specifically to CD137. Scholler also does not teach a method of inducing anti-tumor immunity utilizing a composition comprising a first tumor cell that expresses a cell surface CD83 polypeptide and a second tumor cell that expresses a cell

surface form of an antibody, antigen-binding fragment thereof, that binds specifically to CD137.

However, Ye teaches variable-region genes from the anti-4-1BB (art known as CD183) hybridoma 1D8 and "[t]he scFv gene-fusion construct in pLNCX was transfected into RetroPack PT67 packaging cells, see page 347, Vectors...section. K1735-WT (melanoma cells) were transfected with the said construct, see abstract on page 343. "The transfected cells induced a strong type 1 T-helper cell response...", see abstract. The said construct reads on the second recombinant expression construct. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce a composition comprising a tumor cell that expresses both a cell surface CD83 polypeptide and a cell surface form an antigen-binding fragment thereof that binds specifically to CD137 on tumor cells, as well as implementing two separate tumor cells expressing said molecules in an anti-tumor composition. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both documents, concomitant expression of stimulatory molecules induces immune responses, particularly CD8+ T cells, see Scholler's title and abstract; and Hellstrom, page 71 and 72. Hellstrom notes "...concomitant expression of tumor antigen and anti-CD137 scFv effectively engages NK cells, monocytes and dendritic cells, as well as activated CD4+ and CD8+ T cells ...so as to induce and expand a tumor-destructive Th1 response", page 72, 1st two full sentences in column 1.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The Examiner works a flexible schedule, however she can normally be reached on 8 am to 8 pm, Monday through Saturday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Misook Yu, Ph.D. can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alana M. Harris, Ph.D.
20 December 20, 2010
/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643